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(54) **Buccal administration of estrogens.**

(57) An adequate blood plasma level of 17-beta-estradiol or ethinyl estradiol is attained in a patient in need of estrogen therapy by administration of a dose of 17-beta-estradiol or ethinyl estradiol or a pharmaceutically acceptable ester thereof not greater than 150 micrograms into the vestibule of the buccal cavity of the patient and maintaining the dose in contact with the oral mucosa for a period of time sufficient for transmucosal absorption of a sufficient amount of estrogen to produce a therapeutically effective plasma concentration of estrogen.

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containing a low dosage of these drugs.

Further objects will become apparent from the description of the invention which follows.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

According to the invention an estrogen is administered to the vestibular region of the oral or buccal cavity. The cavity of the mouth (oral cavity or buccal cavity) is comprised of two parts: an outer, smaller portion, the vestibule; and an inner larger part called the mouth cavity proper. The vestibule is a collapsed slit-like space bounded internally by the gums and teeth and externally by the cheek and lips. The vestibule may be further described as having maxillary portions comprising the upper jaw and mandibular portions comprising the lower jaw. Each of these comprises a frontal space between the teeth and gums and the lips and a lateral space located between the teeth and gums and the cheek on each side. The vestibule receives secretions from the paired parotid salivary gland ducts located lateral and dorsal in the maxillary vestibule. This salivary secretion flows over the molars and into the mouth cavity proper. In addition, submandibular (submaxillary) and sublingual salivary glands discharge their secretions into the lower portion of the mouth cavity proper inside the arch formed by the lower teeth. Accordingly, the different portions of the buccal cavity experience different flows of saliva depending on their anatomical relation to the salivary gland ducts.

Consequently, buccal dosage forms which are placed within the mouth cavity proper are exposed to the secretions from all three pairs of salivary glands, and medications released in that location are relatively rapidly washed out of the oral cavity. The flow of saliva in the vestibule of the oral cavity is substantially less than in the mouth cavity proper, and medications released from buccal dosage forms placed within the vestibule of the oral cavity are therefore retained in contact with the oral mucosa for longer periods of time. Dosage forms contained in the frontal mandibular vestibule receive the lowest level of fluid flow of any place in the general cavity of the mouth.

According to the invention it has been found that adequate plasma levels of 17-beta-estradiol or ethinyl estradiol are attained when a dose of 17-beta-estradiol or ethinyl estradiol comprising not more than 150 micrograms of 17-beta-estradiol is administered to the vestibule of the buccal cavity. The estrogen which is brought into contact with the oral mucosa in this region of the oral cavity is absorbed readily through the mucosa and diffuses into the underlying capillary bed from which it enters the bloodstream and is distributed throughout the body. Since a drug administered via the buccal mucosa does not pass immediately through the liver as does a drug absorbed from the intestines, the metabolism which destroys a large portion of 17-beta-estradiol in its first pass through the liver is avoided by this method of administration. At the same time, the greater efficiency of absorption of 17-beta-estradiol through the buccal mucosa as compared with absorption when the drug is administered via the sublingual route permits the dosage to be reduced substantially over that required for sublingual administration. Generally, attaining effective plasma levels of 17-beta-estradiol by sublingual administration requires a dose of at least 200 micrograms. In buccal administration according to this invention, however, effective plasma levels of 17-beta-estradiol are attained with administration of a dose of not more than 150 micrograms, preferably about 100 micrograms of 17-beta-estradiol. A dose of fifty micrograms of 17-beta-estradiol results in a therapeutic plasma level. While it is uncertain why buccal administration according to this invention is more efficient than other transmucosal administration of 17-beta-estradiol, it is believed that the medication is in contact with the mucosa for a longer period of time when administered to the vestibule than when administered sublingually because of the lower rate of salivary flow in the vestibular site.

Within the vestibule of the buccal cavity itself, certain sites are preferred, since it has been found that the rate of flow of saliva which washes the drug away from the point of absorption varies from one location to another within the vestibule. For example the upper vestibule, between the upper gums and the cheek is less preferred because saliva flowing from this location passes to the interior portion of the oral cavity inside the teeth and thus carries dissolved medication away from the buccal mucosa. The lower vestibule between the lower gums and cheek is a preferred location because the flow of saliva which carries away the dissolved drug to the interior of the oral cavity and down the esophagus is less than in the upper vestibule. The most preferred location is the frontal mandibular vestibule, located between the lower front gums and the lower lip generally opposite the second lower lateral incisor and the lower canine teeth. This location has been found to have the lowest rate of flow of saliva in the buccal cavity and therefore, medication delivered to this site is absorbed by the buccal mucosa with greatest efficiency.

A further advantage of buccal administration of estrogen according to this invention is the rapid attaining of therapeutic plasma levels of estrogen. This is useful in the treatment of certain conditions such as the vasomotor disturbances associated with menopause wherein rapid relief is sought.

In order to achieve efficient transmucosal transfer of the hormone in the method of this invention, which results in rapidly attaining therapeutic plasma levels, the 17-beta-estradiol or ethinyl estradiol should be delivered in the form of a very fine dispersion or solution of the drug in a polyethylene glycol matrix. A preferred method of administration is via a rapidly dissolving lozenge, or the like, containing 17-beta-estradiol dispersed in a polyethylene glycol excipient which rapidly dissolves in the saliva of the buccal cavity thereby releasing the 17-beta-estradiol into the buccal cavity close to the buccal mucosa through which it can diffuse to enter the circulation. Suitable dosage forms include lozenges, disks, wafers, tablets and the like. A preferred dosage form comprises a solid matrix of polyethylene glycol (PEG) having 17-beta-estradiol or a pharmaceutically acceptable ester of 17-beta-estradiol dissolved therein. A preferred dosage form comprises 17-beta-estradiol

dissolved in a mixture of polyethylene glycols comprising a relatively low molecular weight PEG having a molecular weight not greater than about 4000 daltons and a relatively high molecular weight PEG having a molecular weight of about 6000 to about 20,000 daltons. The proportions of low molecular weight PEG and high molecular weight PEG are chosen to provide a melting point of about 50°-70° C. The drug composition for making the dosage forms is prepared by dissolving the drug in the molten mixture of PEG's, then solidifying the mixture by cooling to room temperature. Dosage forms may be prepared by introducing the molten drug composition into suitable molds and chilling the composition therein, or by casting a thin film of the composition on a chilled metal plate and cutting dosage forms of the proper size from the cast film. A preferred dosage form for use in practicing the method of this invention is a wafer weighing about 25-300 milligrams and containing 50-150 micrograms, preferably about 100 micrograms of 17-beta-estradiol.

The desired plasma level of estrogen which is to be attained by the method of this invention will depend on the purpose of the administration. Estrogen is administered as replacement therapy in post-menopausal women to relieve post-menopausal syndrome and to prevent osteoporosis. While the extent amount of estrogen needed to prevent osteoporosis is unknown, it is thought to be about 50 to 100 micrograms per day, which would correspond approximately to a plasma maximum level of about 250-500 picograms/milliliter of 17-beta-estradiol. For treatment of post-menopausal syndrome, it may be desirable to increase the dosage to 200-400 micrograms per day, which corresponds approximately to the daily production of estrogen in premenopausal women.

Evidently, the buccal administration of 17-beta-estradiol, which avoids first-pass metabolism in the liver, corresponds more nearly to the natural production of 17-beta-estradiol in the body. The rapid availability of estrogen administered by the buccal route may also be advantageous because the rapidly attained high peak values of plasma concentration tend to produce a greater saturation of the 17-beta-estradiol receptors in tissues than a lower concentration achieved, e.g., by oral administration.

The buccal route has also been found effective for administration of esters of 17-beta-estradiol which are used in therapy, e.g., 17-beta-estradiol cypionate, 17-beta-estradiol valerate and the like. Synthetic estrogens, such as ethinyl estradiol can also be used in the method of this invention, since liver first pass destruction is thought to be about 70 %.

The invention will be further illustrated by the following exampleS which is not intended to be limiting.

EXAMPLE 1

The effectiveness of the buccal administration of 17-beta-estradiol is illustrated in the following example.

Buccal dosage forms were prepared by the following process. 17-Beta-estradiol was dissolved in a molten mixture of equal parts of PEG 3350 and PEG 6000 at a temperature of 60° C and the resulting solution was cast into a thin film on a chilled metal plate to form a solid thin film of a solid solution of 17-beta-estradiol in a mixed PEG matrix. Buccal dosage forms in the shape of thin wafers were cut from the film of a size to contain 100 micrograms of 17-beta-estradiol each.

A comparative test of plasma levels of 17-beta-estradiol attained by buccal versus oral administration was conducted by the following procedure. A buccal dose of 100 micrograms of 17-beta-estradiol was administered to each of four test subjects by having each subject place one of the dosage forms prepared as described above in the buccal cavity between the cheek and gum. A fifth subject received a dose of 200 micrograms in the same way. The subjects were all ovariectomized women, and the plasma estrogen levels of the subjects were monitored for a few days prior to the test and determined to be very low. 17-Beta-estradiol plasma levels were monitored periodically after the dose was administered. The results are tabulated in Table 1, and show that plasma levels of 17-beta-estradiol (E_2) in these subjects increased rapidly, reaching peak concentration at 30-45 minutes after administration with peak plasma levels reaching 384 picograms/milliliter. Plasma levels decreased to near pretreatment levels after eight hours.

After a suitable washout interval, the same four subjects were given oral doses of 500 to 1000 micrograms of 17-beta-estradiol by swallowing five to ten of the dosage forms prepared as described above. The results are also tabulated in Table 1 and show that peak plasma levels of 17-beta-estradiol were reached in 15-30 minutes after administration with average 17-beta-estradiol concentrations reaching 185 picograms/milliliter.

Table 1 also includes the data for peak values of estrone (E_1), a less active metabolite of 17-beta-estradiol, and the times to attain the peak values of estrone. The data show that for estrone also buccal administration is substantially more efficient than oral administration. The results of this experiment demonstrate that therapeutically effective plasma levels of estrogen can be achieved by buccal administration of as little as 100 micrograms of 17-beta-estradiol.

The results of this experiment indicate that the buccal route of administration is much more efficient than the oral route and can provide plasma levels of 17-beta-estradiol equivalent or greater than those achieved by oral doses five to ten times greater.

Furthermore, the results of this experiment show improvement over the administration of estrogens as complexes with cyclodextrins as taught by Pitha, U.S. Patent 4,596,795. Figure 1 of the Pitha reference shows the results of sublingual administration of 0.5 milligrams (500 micrograms) of 17-beta-estradiol in the form of a complex with a cyclodextrin. Pitha's data show that a plasma level of about 115 picograms per milliliter was attained one hour after administration. In the experiment of this example a dose of 100-200 micrograms administered by the method of this invention produced an average plasma levels of 385 picograms per milliliter 30-45 minutes after administration. Evidently, the method of administering an estrogen according to this

invention is substantially more efficient since it achieves greater plasma levels with lower doses of estrogen.

TABLE 1

Patient/dose	Estradiol (E_2) peak pg/ml	Time to estradiol (E_2) peak min	Estrone (E_1) peak pg/ml	Time to estrone (E_1) peak min
W.C.				
200 ug buccal	374	30	77	30
1000 ug oral	265	15	136	120
S.C.				
100 ug buccal	555	30	126	60
800 ug oral	375	15	349	60
E.D.				
100 ug buccal	304	30	69	120
500 ug oral	123	15	81	60
R.H.				
100 ug buccal	440	30	128	30
800 ug oral	94	30	200	120
T.S.				
100 ug buccal	251	45	137	60
800 ug oral	69	30	173	240
Average or range:				
100-200 ug buccal	385	30-45	107	30-120
500-1000 ug oral	185	15-30	188	60-240

EXAMPLE 2

This example illustrates the plasma level of estrogen attainable with a very low buccal dose.

A dose of 50 micrograms of 17-beta-estradiol was administered to a male volunteer subject by the buccal administration procedure of Example 1. The plasma level of 17-beta-estradiol reached a maximum of 290 picograms per milliliter in 30 minutes, while the estrone plasma level reached a maximum of 70 picograms per milliliter in 120 minutes. This result indicates that therapeutic levels of estrogen can be achieved using a dose of estrogen as small as 50 micrograms when administered by the method of this invention.

The invention having now been fully described, it should be understood that it may be embodied in other specific forms or variations without departing from its spirit or essential characteristics. Accordingly, the embodiments described above are to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Claims

1. A buccal dosage form for the transmucosal administration of estrogen to a human comprising not more than 150 micrograms of an estrogen selected from the group consisting of 17-beta-estradiol and ethinyl estradiol or a pharmaceutically equivalent amount of a non-toxic pharmaceutically acceptable ester thereof in a pharmaceutically acceptable non-toxic solid excipient.

2. The buccal dosage form of Claim 1 comprising not more than 50 or 100 micrograms of said estrogen.

3. The buccal dosage form of Claims 1 or 2 wherein said excipient comprises a polyethylene glycol.

4. The buccal dosage form of Claims 1 to 3 wherein said excipient comprises a mixture of polyethylene glycols.

5. The buccal dosage form of Claims 1 to 4 wherein said mixture of polyethylene glycols comprises at least one low molecular weight polyethylene glycol and at least one medium or high molecular weight polyethylene glycol.

6. The buccal dosage form of Claims 1 to 5 wherein the estrogen or ester thereof is in the form of a dispersion in a water-soluble solid polyethylene glycol or mixture of water-soluble solid polyethylene glycols.

7. The buccal dosage form of Claim 6, wherein the dispersion is a solid solution of said estrogen or ester thereof in the water-soluble solid polyethylene glycol or mixture of water-soluble solid polyethylene glycols.

8. The buccal dosage form of Claims 6 and 7 wherein said mixture of water-soluble solid polyethylene glycols is a mixture of a low molecular weight polyethylene glycol and a medium or high molecular weight polyethylene glycol.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 73 0081

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	FR-M- 6 955 (E. BOUCHARA) * Examples 1,2; abstract *	1,2	A 61 K 31/565 A 61 K 47/00 A 61 K 9/20
X,P	WO-A-8 704 342 (KEY PHARMACEUTICALS INC.) * Claims 1-4 *	1-3	
D,Y	EP-A-0 107 941 (TAKEDA CHEMICAL INDUSTRIES LTD) * Page 9, lines 1-12; page 5, line 2 *	1-8	
P,Y	EP-A-0 232 877 (ZETACHRON INC.) * Page 5, lines 14-21; examples 20,21; claims 1-13 *	1-8	
.Y	US-A-3 009 857 (F.X. GASSNER et al.) * Example 17 *	1-8	
A	US-A-2 698 822 (A. HALPERN et al.) * Claims 1-5 *		

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11-07-1988	TZSCHOPPE, D.A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
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